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INTERNATIONAL APPLICATION PUBLISHEI

WO 9602546A1

(51) International Patent Classification 6 :
C07D 491/22, A61K 31/47 A

(43) International Publication Date: 1 February 1996 (01.02.96)

(21) International Application Number: PCT/US95/08786

(22) International Filing Date: 20 July 1995 (20.07.95)

(30) Priority Data:
08/277,642 20 July 1994 (20.07.94) US

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(81) Designated States: AU, CA, JP, KR, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

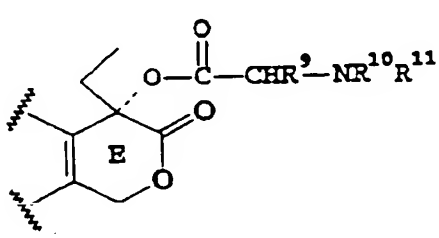
(54) Title: WATER-SOLUBLE ESTERS OF CAMPTOTHECIN COMPOUNDS

(57) Abstract

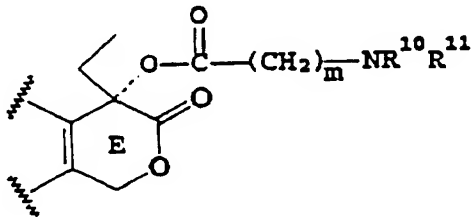
Non-toxic camptothecin prodrugs are prepared by esterifying the 20-position hydroxyl group of camptothecin derivatives.

WHAT IS CLAIMED AS NEW AND IS DESIRED TO BE SECURED BY LETTERS PATENT OF THE UNITED STATES IS:

1. A method for reducing the toxicity of a camptothecin compound, comprising esterifying the hydroxyl group at the 20-position of the E-ring of a camptothecin compound to form a camptothecin compound in which the E-ring has the formula:

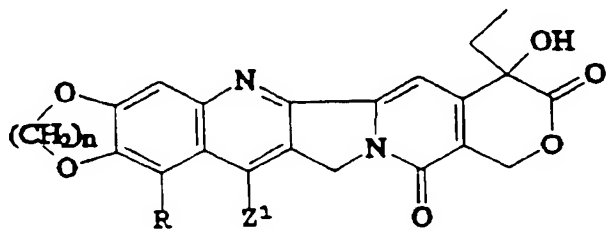


or



wherein m = 1-6, R^9 is the side chain of one of the naturally occurring α-amino acids, R^{10} and R^{11} are, independently, hydrogen or C_{1-8} alkyl, with the proviso that the camptothecin compound is not camptothecin or camptothecin substituted on the A-ring thereof with an alkyl group or with a substituted alkyl group as found in natural amino acids.

2. The method of Claim 1, wherein said camptothecin compound has the structure shown below

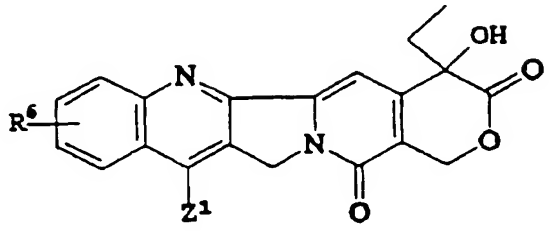


wherein R is NO_2, NH_2, N_3, hydrogen, halogen, COOH, OH, O-C_{1-3} alkyl, SH, S-C_{1-3} alkyl, CN, CH_2NH_2, NH-C_{1-3} alkyl, CH_2-NH-C_{1-3} alkyl, N(C_{1-3} alkyl)$_2$, $CH_2N(C_{1-3}$ alkyl)$_2$, O-, NH- and S-$CH_2CH_2N(CH_2CH_2OH)_2$, O-, NH- and S-$CH_2CH_2CH_2N(CH_2CH_2OH)_2$, O-, NH- and S-$CH_2CH_2N(CH_2CH_2CH_2OH)_2$, O-, NH- and S-$CH_2CH_2CH_2N(CH_2CH_2CH_2OH_2)_2$, O-, NH- and S-$CH_2CH_2N(C_{1-3}$ alkyl)$_2$, O-, NH- and S-$CH_2CH_2CH_2N(C_{1-3}$ alkyl)$_2$, CHO or C_{1-3} alkyl;

Z^1 in the structure shown above is H, C_{1-8} alkyl, or $CH_2NR^1R^2$ where (a) R^1 and R^2 are, independently, hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl-C_{1-6} alkyl, C_{2-6} alkenyl, hydroxy-C_{1-6} alkyl, C_{1-6} alkoxy-C_{1-6} alkyl, (6) R^1 is hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl-C_{1-6} alkyl, C_{2-6} alkenyl, hydroxy- C_{1-6} alkyl or C_{1-6} alkoxy-C_{1-6} alkyl and R^2 is $-COR^3$ where R^3 is hydrogen, C_{1-6} alkyl, perhalo-C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl-C_{1-6} alkyl, C_{2-6} alkenyl, hydroxy-C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxy-C_{1-6} alkyl, or (c) R^1 and R^2 taken together with the nitrogen atom to which they are attached form a saturated 3-7 membered heterocyclic ring which may contain a O, S or NR^4 group, where R^4 is hydrogen, C_{1-6} alkyl, perhalo-C_{1-6} alkyl, aryl, aryl substituted with one or more groups selected from the group consisting of C_{1-6} alkyl, halogen, nitro, amino, C_{1-6} alkylamino, perhalo-C_{1-6} alkyl, hydroxy-C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxy-C_{1-6} alkyl and $-COR^5$ where R^5 is hydrogen, C_{1-6} alkyl perhalo-C_{1-6} alkyl, C_{1-6} alkoxy, aryl, and aryl substituted with one or more C_{1-6} alkyl, perhalo-C_{1-6} alkyl, hydroxy-C_{1-6} alkyl, or C_{1-6} alkoxy-C_{1-6} alkyl groups;

n is an integer of 1 or 2; and pharmaceutically acceptable [illegible] thereof.

3. The method of Claim 1, wherein said camptothecin compound has the structure shown below



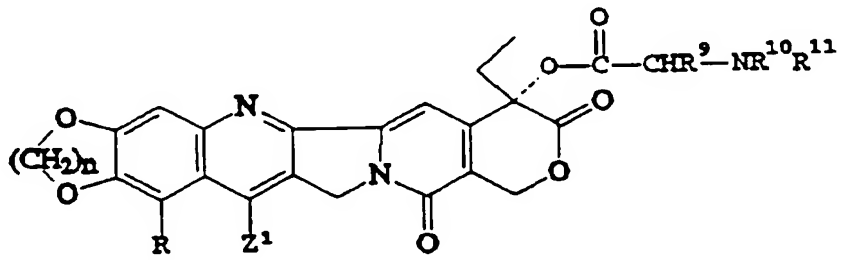
wherein R^6 is cyano, formyl, hydroxy, C_{1-8} alkoxy, nitro, amino, halogen, trifluoromethyl, aminomethyl, azido, amido, hydrazino, $OC(O)R^7$ or $OC(O)NR^7R^8$ where R^7 and R^8 are, independently, hydrogen or C_{1-8} alkyl; and

Z^1 is H, C_{1-8} alkyl, or $CH_2NR^1R^2$ where (a) R^1 and R^2 are, independently, hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl-C_{1-6} alkyl, C_{2-6} alkenyl, hydroxy-C_{1-6} alkyl, C_{1-6} alkoxy-C_{1-6} alkyl, (6) R^1 is hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl-C_{1-6} alkyl, C_{2-6} alkenyl, hydroxy- C_{1-6} alkyl or C_{1-6} alkoxy-C_{1-6} alkyl and R^2 is $-COR^3$ where R^3 is hydrogen, C_{1-6} alkyl, perhalo-C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl-C_{1-6} alkyl, C_{2-6} alkenyl, hydroxy-C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxy-C_{1-6} alkyl, or (c) R^1 and R^2 taken together with the nitrogen atom to which they are attached form a saturated 3-7 membered heterocyclic ring which may contain a O, S or NR^4 group, where R^4 is hydrogen, C_{1-6} alkyl, perhalo-C_{1-6} alkyl, aryl, aryl substituted with one or more groups selected from the group consisting of C_{1-6} alkyl, halogen, nitro, amino, C_{1-6} alkylamino, perhalo-C_{1-6} alkyl, hydroxy-C_{1-6} alkyl, C_{1-6} alkoxy-C_{1-6} alkyl and $-COR^5$ where R^5 is

substituted with one or more C_{1-6} alkyl, perhalo-C_{1-6} alkyl, hydroxy-C_{1-6} alkyl, or C_{1-6} alkoxy-C_{1-6} alkyl groups.

4. The method of Claim 1, wherein said camptothecin compound is selected from the group consisting of 9-amino-10,11-methylenedioxy-20(S)-camptothecin, 9-chloro-10,11-methylenedioxy-(20S)-camptothecin, 10,11-methylenedioxy-20(S)-camptothecin, 9-chloro-20(S)-camptothecin, 7-methyl-10, 11-methylenedioxy-20(S)-camptothecin, 7-ethyl-10,11-methylenedioxy-20(S)-camptothecin, 7-chloromethyl-10,11-methylenedioxy-20(S)-camptothecin, 9-amino-20(S)-camptothecin, 10-amino-20(S)-camptothecin, and 10-chloro-20(S)-camptothecin.

5. A camptothecin ester having the structure:



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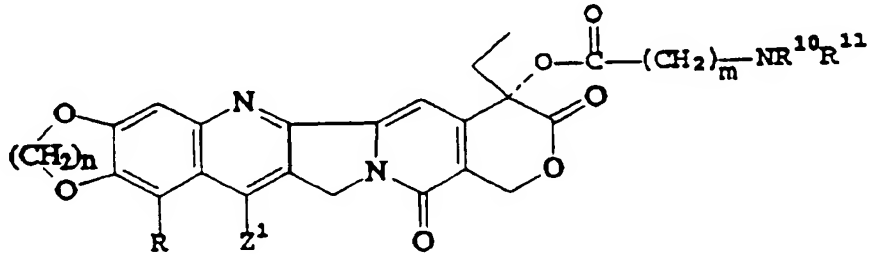
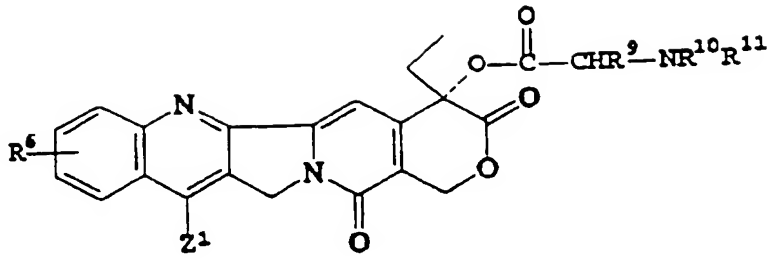
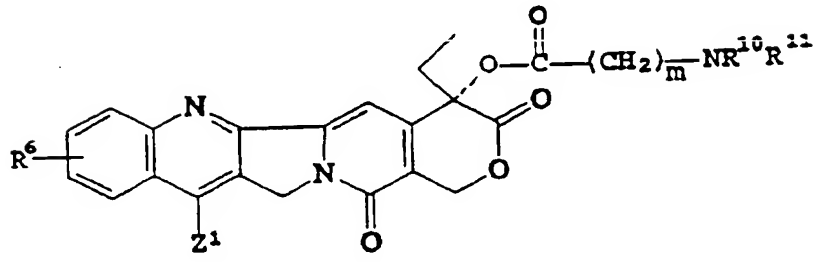


or



or



wherein

R is NO_2, NH_2, N_3, hydrogen, halogen, COOH, OH, O-C_{1-3} alkyl, SH, S-C_{1-3} alkyl, CN, CH_2NH_2, NH-C_{1-3} alkyl, CH_2-NH-C_{1-3} alkyl, N(C_{1-3} alkyl)$_2$, $CH_2N(C_{1-3}$ alkyl)$_2$, O-, NH- and S-$CH_2CH_2N(CH_2CH_2OH)_2$, O-, NH- and S-$CH_2CH_2CH_2N(CH_2CH_2OH)_2$, O-, NH- and S-$CH_2CH_2N(CH_2CH_2CH_2OH)_2$, O-, NH- and S-$CH_2CH_2CH_2N(CH_2CH_2CH_2OH_2)_2$, O-, NH- and S-$CH_2CH_2N(C_{1-3}$ alkyl)$_2$, O-, NH- and S-$CH_2CH_2CH_2N(C_{1-3}$ alkyl)$_2$, CHO or C_{1-3} alkyl;

Z^1 is H, C_{1-8} alkyl, or $CH_2NR^1R^2$ where (a) R^1 and R^2 are, independently, hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl-C_{1-6} alkyl, C_{2-6} alkenyl, hydroxy-C_{1-6} alkyl, C_{1-6} alkoxy-C_{1-6} alkyl, (6) R^1 is hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7}

alkoxy-C_{1-6} alkyl and R^2 is $-COR^3$ where R^3 is hydrogen, C_{1-6} alkyl, perhalo-C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl-C_{1-6} alkyl, C_{2-6} alkenyl, hydroxy-C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxy-C_{1-6} alkyl, or (c) R^1 and R^2 taken together with the nitrogen atom to which they are attached form a saturated 3-7 membered heterocyclic ring which may contain a O, S or NR^6 group, where R^6 is hydrogen, C_{1-6} alkyl, perhalo-C_{1-6} alkyl, aryl, aryl substituted with one or more groups selected from the group consisting of C_{1-6} alkyl, halogen, nitro, amino, C_{1-6} alkylamino, perhalo-C_{1-6} alkyl, hydroxy-C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxy-C_{1-6} alkyl and $-COR^5$ where R^5 is hydrogen, C_{1-6} alkyl perhalo-C_{1-6} alkyl, C_{1-6} alkoxy, aryl, and aryl substituted with one or more C_{1-6} alkyl, perhalo-C_{1-6} alkyl, hydroxy-C_{1-6} alkyl, or C_{1-6} alkoxy-C_{1-6} alkyl groups;

R^6 is cyano, formyl, hydroxy, C_{1-8} alkoxy, nitro, amino, halogen, trifluoromethyl, aminomethyl, azido, amido, hydrazino, $OC(O)R^7$ or $OC(O)NR^7R^8$ where R^7 and R^8 are, independently, hydrogen or C_{1-8} alkyl;

m is an integer of 1 to 6; and

n is an integer of 1 or 2; and pharmaceutically acceptable salts thereof.

6. A pharmaceutical composition, comprising the camptothecin ester of Claim 5 and a pharmaceutically acceptable carrier or diluent.

7. A method of forming a topoisomerase I inhibiting camptothecin compound in a mammal comprising administering the camptothecin ester of Claim 5 to a mammal in an amount sufficient to inhibit topoisomerase I.

mg/kg body weight per week of camptothecin ester.

9. The method of Claim 7, wherein said administering is oral or parenteral administering.

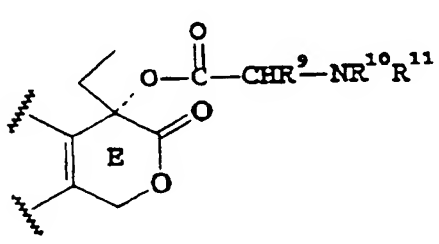
10. A method of treating leukemia or solid tumors in a mammal in need thereof, comprising administering to said mammal an effective amount for treating said tumor of the camptothecin ester of Claim 5.

11. The method of Claim 10, comprising administering 1-80 mg/kg body weight per week of camptothecin ester.

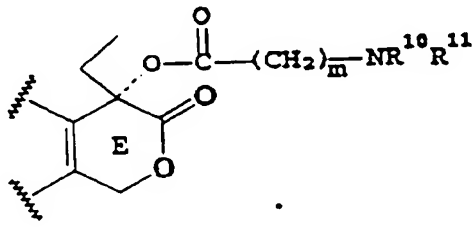
12. The method of Claim 10, wherein said administering is oral or parenteral administering.

13. The method of Claim 10, wherein said method is a method of treating a colon, lung or breast solid tumor.

14. A method of extending the in vivo systemic lifetime of a camptothecin compound in a mammal, comprising esterifying the hydroxyl group at the 20-position of the E-ring of a camptothecin compound to form a camptothecin compound in which the E-ring has the formula:



or



.

wherein m = 1-6, R^9 is the side chain of one of the naturally occurring α-amino acids, R^{10} and R^{11} are, independently, hydrogen or C_{1-8} alkyl, with the proviso that the camptothecin compound is not camptothecin or camptothecin substituted on the A-ring thereof with an alkyl group or with a substituted alkyl group as found in natural amino acids.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/08786

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07D 491/22; A61K 31/47
US CL :546/41, 48; 514/279, 283

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 546/41, 48; 514/279, 283

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS Online Structure Search
CA File Word Search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US, A, 4,943,579 (VISHNUVAJJALA ET AL.) 24 July 1990, see column 4, line 1 - column 7, line 45 and claims 1-3.	1-6, 14 --- 7-13
A, P	US, A, 5,352,789 (HINZ) 04 October 1994, see column 6, lines 38-55.	1-14
Y	US, A, 5,004,758 (BOEHM) 02 April 1991, see column 1, lines 46-51.	1-14
Y	US, A, 5,106,742 (WALL ET AL.) 21 April 1992, see claims 1-3.	2, 5-14
Y	US, A, 4,604,463 (MIYASAKA ET AL.) 05 August 1986, see column 2, lines 54-8, column 5, lines 10-50.	1-14

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be part of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

[illegible] priority date claimed

[illegible] the international search

19 OCTOBER 1995

28 NOV 1995

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
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Washington, D.C. 20231

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D G DAUS acó

Facsimile No. (703) 305-3230

Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/08786

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JOURNAL OF MEDICINAL CHEMISTRY, Vol. 36, No. 18 issued 03 September 1993, WALL, ET AL. "PLANT ANTITUMOR AGENTS, 30 SYNTHESIS AND STRUCTURE ACTIVITY OF NOVEL CAMPTOTHECIN ANALOGS", pages 2689-2700, see page 2690 compounds 7e to 7i, page 2692 Table II compounds 7i, 7g, Table IV, 7i and 7g, page 2693 Table VI, cpds. 7g, 7l, 7j, page 2692, column 1 through last paragraph, column 2 for esterification processes. Note footnote 1(b), page 2699, for oral disclosure, April 1992. See also page 2691, first column, fifth paragraph and page 2699 third paragraph.	1-14
X, P	DERWENT WPIDS ABSTRACT OF WO 95-10304, (PHARMACIA SPA) 02 June 1995. See lines 13-15.	1-14

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/08786

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/08786

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

Group I. Claims 1-4 and 14, drawn to methods for esterifying CPT;
Claims 5-6 drawn to CPT ester compound, composition.
Claims 7-9 drawn to a first method of using II to form another unspecified compound in vivo.
Group II.Claims 10-13 drawn to a second method of using II for leukemia or tumors.
This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.
The inventions listed as Groups I to II do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:
The second method of use of a first composition has no nexus with first method of use for forming a topoisomerase I and it considers that the International Application does not comply with the requirements of unity of invention (Rules inhibiting compound in vivo 13.1, 13.2, and 13.30 for the reasons indicated below:
Only the first appearing method of use of the first product is grouped with the first product pursuant to 37 CFR 1.475(d).